High Incidence and Regression Rates of Solar Keratoses in a Queensland Community

Christine Frost,*† Gail Williams,‡ and Adele Green†

*Serono Australia Pty. Ltd, Sydney, †Epidemiology and Population Health Unit, Queensland Institute of Medical Research, Brisbane, Australia; ‡Australian Center for International and Tropical Health and Nutrition, University of Queensland, Brisbane, Australia

The presence of solar keratoses on the skin is one of the major risk factors for basal cell and squamous cell carcinomas, which constitute a growing public health problem in today's white populations. In spite of this, little is known of the natural history of solar keratoses. We conducted follow-up studies to monitor the incidence, regression, and recurrence rates of solar keratoses in a random sample (N = 96) of the Nambour community in Queensland. At baseline, 43 participants (46%) were diagnosed with at least one solar keratosis [26 men (55%), 17 women (37%)] with a total count of 494 prevalent solar keratoses. The distribution of lesions per person was highly skewed, with 11 individuals (12%) having 65% of the total number of solar keratoses. During 12 mo of follow-up, 614 incident solar keratoses were diagnosed (549 in men and 65 in women); 526 solar keratoses regressed and 53 prevalent solar keratoses recurred, giving a net 45% increase in solar keratosis numbers in men (from 354 to 512 solar keratoses) and a net 44% reduction in women (from 114 to 64). Regression rates were higher in prevalent (74%) than incident (29%) solar keratoses. Solar keratosis prevalence increased with age in both sexes, and individuals with solar keratoses at baseline were over seven times more likely to develop additional solar keratoses in the next 12 mo than those without prevalent solar keratoses at baseline. These results show that the natural history of solar keratoses in the community is one of high turnover and that a small percentage of susceptible individuals carry the major burden of solar keratoses in the community. ***Key words: epidemiology/skin cancer. J Invest Dermatol 115:273–277, 2000***

Solar keratoses (SK), basal cell carcinomas (BCCs), and squamous cell carcinomas (SCCs) of the skin constitute a growing public health problem in pale-skinned populations (Miller and Weinstock, 1994). Incidence of BCC and SCC in Australia is estimated to be in excess of 1000 per 100,000 people per y, resulting in at least 150,000 people developing these skin cancers annually. During the decade from 1985 to 1995, SCC rates in Australia rose by 93% from 166 to 321 per 100,000, and BCCs from 657 to 788 per 100,000 (a 19% increase) (Staples *et al*, 1998). SK bear a strong histologic and epidemiologic resemblance to SCCs and are among the strongest predictors of skin cancer (Green and Battistutta, 1990), yet few published epidemiologic data about SK exist. These lesions are intermediate biomarkers of skin cancer but very little is known of their natural history. Such data are important to better understand the pathogenesis of skin cancer, and to provide a baseline against which to evaluate the preventive strategies currently recommended by public health authorities.

In a follow-up study of SK among a random sample of 560 elderly subjects from South Wales (Harvey *et al*, 1996a), baseline prevalence was 23% and 83 new SK were diagnosed in 49 subjects at a second visit 1–2 y later (median 1.43 y). This equates to incidence rates of 88 persons affected per 1000 person years and 149 SK tumors per 1000 person years. Spontaneous regression occurred in 50 of 239 SK (21%, 95% confidence interval (95% CI) 16%–26%).

The only other reported longitudinal studies of SK were conducted in Australia (Marks *et al*, 1986; 1988). In the first study, 1040 volunteers aged ≥ 40 y were seen on two occasions 12 mo apart. On initial examination, 616 subjects (59%) were diagnosed with SK, 60% of whom had developed new SK at the 12 mo visit. In comparison, 81 (19%) of the 424 people without SK at baseline were diagnosed with new lesions after 12 mo. In total, 485 of 873 SK (26%) diagnosed at baseline underwent spontaneous regression (Marks *et al*, 1986). In a subsequent 5 y prospective study, Marks *et al* (1988) found (on mapping both SCCs and pre-existing SK) that 10 of 17 SCCs (60%) arose in a lesion that previously had been clinically diagnosed as an SK. With a total of 21,905 SK recorded at the initial visit, this represents a malignant transformation rate of less than 1 in 1000 per y.

Although these studies provide important information, the data were collected on only two occasions separated by relatively long periods of time. To obtain deeper insight into the natural history of SK, a more intensive follow-up study, the Nambour SK study, was commenced in 1992. We report here the first detailed account of the incidence, regression, and recurrence rates of SK in a community.

MATERIALS AND METHODS

Subjects Participants in the Nambour SK study were a subset of participants in an Australian field trial of prevention of skin cancer (the Nambour Trial) (Green *et al*, 1994). All participants in the Nambour Trial

Manuscript received January 6, 2000; revised April 18, 2000; accepted for publication May 8, 2000.

Reprint requests to: Dr. Christine Frost, c/o Lynn Green, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Queensland 4029, Australia. Email: chris_frost_au@yahoo.com

Abbreviations: BCC, basal cell carcinoma; SK, solar keratosis.

Table I. Baseline characteristics

Variable	Categories	Number	Proportion
Age (y)	30–39	21	0.22
	40–49	24	0.25
	50–59	23	0.24
	60–69	28	0.29
Sex	Male	48	0.50
	Female	48	0.50
Natural skin color	Fair	65	0.68
	Medium	24	0.25
	Olive	7	0.07
	Black	0	0.00
Tanning ability	Always burn, never tan	21	0.22
	Burn then tan	64	0.67
	Only tan	11	0.11
Educational level	$\leqslant 10$ y	39	0.41
	11-12 y	6	0.06
	Other qualification	36	0.38
	Degree	6	0.06
	Other	9	0.09

had been randomly selected in 1986 from residents of Nambour, a subtropical township that lies 100 km north of Brisbane, Queensland, at latitude 26°S. The Nambour Trial commenced in 1992, when 1626 adults aged between 25 and 75 y were randomized using a 2×2 factorial design to apply daily sunscreen to the skin of the head, neck, hands, and forearms, or not, and to take 30 mg beta-carotene or placebo tablets daily (Green *et al*, 1999).

In mid-1992 an age-stratified random sample of 201 subjects was selected for the Nambour SK study and 200 agreed to take part. Of these, three subjects who had a diagnosis of disseminated superficial actinic porokeratosis were excluded. Only those 96 subjects not assigned to the sunscreen intervention arm of the Nambour Trial (Green *et al*, 1999) were included in the SK study (of whom 49% were receiving supplementary beta-carotene and 51% placebo). Subjects assigned to supplementary beta-carotene were not excluded as there is no evidence linking it to SK development. Baseline characteristics of the participants are shown in **Table I**.

Data collection Half the subjects were randomized to 2-monthly examinations for a period of 14 mo, and half to 6-monthly examinations for 18 mo. At each visit, skin examinations of the head, neck, hands, and forearms were conducted by a single medically qualified investigator (CF) who was additionally trained by dermatologists in the diagnosis of SK and skin cancer. The positions of all SK were recorded on a skin grid-map printed on clear plastic. This grid-map was ''moulded'' to the skin of the hands or forearms, thereby maximizing the accuracy of mapping, whereas facial lesions were (by necessity) recorded freehand. The validity of the clinical diagnosis of SK in this study was assessed in a histologic validation study undertaken among 22 study participants.

Definitions of prevalent, incident, regressed, and recurrent SK An SK was defined as a discrete, irregularly scaly (keratotic) lesion with or without pigmentation and/or erythema occurring on a background of solar damaged skin (Frost *et al*, 1998). A prevalent SK was an SK diagnosed on a person during their first skin examination, whereas an incident SK was a lesion appearing for the first time at a position where no SK had previously been diagnosed during the course of the study. A regression occurred whenever a previously documented SK was not clinically apparent at any subsequent visit (i.e., an SK could only be incident on one occasion, but could regress more than once). Although it is possible that a biopsy of the site of a regressed lesion may have revealed histologic evidence of an SK, histologic confirmation was considered neither practical nor ethical. A recurrent SK was recorded if an SK clinically reappeared at the site of a previous regression at any time during follow-up. As for regressions, an SK could recur more than once.

Data analysis In order to gain an accurate picture of the natural history of SK it was necessary to account for all treated SK. During analysis, all SK treated during the period of follow-up were censored from the time of treatment onwards, regardless of whether they subsequently recurred. Participants with lesions suspected of being skin cancers were referred to their local general practitioners for further management.

With an expected annual incidence of 35% of persons developing at least one SK, and an average of 5.5 SK per participant in the Nambour Trial, the number of SK to be monitored throughout the study period was calculated to be in excess of 1100. To accomplish this, a computer program was designed that allowed graphical representations of consecutive skin grid-maps to be superimposed on-screen. This enabled prevalent, incident, recurrent, and regressed SK to be identified and quantified at each follow-up time point. The location of lesions relative to each other was used to orient consecutive skin maps, and an SK had to lie within 0.5 cm of its previously documented location to be considered the same lesion.

In order to verify the accuracy of the computerized examination data, 60 anatomic sites on eight randomly selected subjects were chosen for double entry. Of 1672 lesions originally manually recorded in these subjects during the period of follow-up, only two lesions had not been entered into the computerized mapping program.

In addition to describing subject-specific information regarding the number and distribution of incident, regressed, and recurrent SK, the time from when an SK became clinically apparent to its subsequent regression was estimated. The aim here was to estimate their natural life span, which could be utilized subsequently as an additional indicator of the effectiveness of preventive measures.

Unless otherwise stated, only those visits carried out at 0, 6, and 12 mo were used to calculate the relevant measures. This allowed pooling of information obtained from subjects seen every 6 mo with that from subjects seen every 2 mo. Meanwhile data from subjects assigned to 2-monthly follow-up were examined separately to assess the effect of the frequency of follow-up on accuracy of monitoring SK.

In calculating 95% CIs for SK site distribution, the clustering effect for SK was estimated and used as a multiplier for the standard error calculated using binomial assumptions (Cochrane, 1977).

RESULTS

In subjects with more than 50 SK diagnosed on any one anatomic site, or where more than 50% of the skin on a site was judged to consist of confluent SK, individual lesions could not be distinguished and recorded. These subjects were excluded from those analyses that required an exact count of SK present in order to determine the number of incident, regressed, and recurrent lesions. In total, six participants were diagnosed with more than 50 SK on one site at some stage during follow-up.

Validity of clinical diagnosis Of 22 randomly chosen clinically diagnosed SK (one on each of 22 participants), 20 were confirmed after independent histologic diagnosis by a single dermatopathologist. Of the two lesions incorrectly clinically diagnosed as SK, one was histologically identified as a superficial BCC, and the other as an intraepidermal carcinoma.

Follow-up rates Of a potential 572 scheduled visits to the 96 participants (376 in the 47 subjects being seen 2 monthly, and 196 in the 49 being seen 6 monthly), 533 (93%) were completed. The majority of missed visits were due to subject withdrawal (five subjects, 19 visits) and migration from the follow-up area (two subjects, five visits), with the remaining missed visits being due to temporary absence or illness.

Treated SK During the course of the study, seven subjects (14%, four men and three women) with at least one SK reported having SK treated either by their general practitioner or a dermatologist. In total 93 SK were treated, representing 6% of the total number of SK diagnosed (treatment of two men accounted for 78% of all treated SK). The majority of the lesions treated were located on the hands and forearms (69%) with the remaining 31% being on the head and neck. Neither the percentage of SK treated nor the percentage of individuals reporting treatment differed between the sexes.

SK prevalence Of the 93 eligible subjects seen on visit one, 43 (46%) were diagnosed with at least one SK, yielding a prevalence of 55% in men (95% CI 41%–70%) and 37% in women (95% CI 23%–51%). The percentage of participants with prevalent SK increased with age in both sexes, and within each age group prevalence was generally higher in male participants, ranging from 8% in women and 22% in men aged 30–39 y, up to 64% in women and 83% in men aged 60–69 y.

Table II. Solar keratoses are more prevalent in males than females[a]

Category of solar keratoses[b]	Males (n = 47)	Total no. of solar keratoses[c] (n = 378)	Females (n = 46)	Total no. of solar keratoses[c] (n = 116)
Nil	21	0	29	0
1–10	12	31	13	38
11–20	5	72	2	30
21+	9	275	2	48

[a]The data are based on 93 randomly selected residents of Nambour, Queensland examined at baseline.
[b]Number of prevalent of solar keratoses per individual given by category.
[c]Total number of prevalent solar keratoses.

A total of 494 prevalent SK were diagnosed in the subjects with SK at baseline, 378 in men (77%) and 116 in women (24%) (**Table II**). The distribution of lesions per person was highly skewed, with 11 subjects (12%) having 65% of the total number of SK. In men, nine subjects had 73% of SK, whereas in women, two subjects had 41% of the total number of prevalent SK. The number of SK tended to be higher in older subjects, with approximately 60%–70% of all prevalent SK at baseline being seen in subjects aged over 50 y.

At the gross anatomic level, the distribution of prevalent SK was similar in men and women, with approximately 40% of SK being diagnosed on the head and neck, and the remaining 60% on the hands and forearms (**Fig 1**).

Change in prevalence To calculate the overall change in SK prevalence (number of subjects with at least one SK), and the change in SK numbers over a 12 mo period, only those 89 subjects with information recorded for visits at 0, 6, and 12 mo were included. In men, there was a slight decrease in SK prevalence from 56% in winter 1992 to 51% in winter 1993, though there was a 45% increase in SK numbers on affected persons during the same time period (from 354 to 512 SK). In women, although there was no change in prevalence at 12 mo (36% at both time points), there was a decrease in the total number of SK recorded, from 114 to 64 (a 44% reduction). Despite the change in SK numbers, no apparent seasonal variation in the occurence of incident or regressed SK in men or women was recorded during the 6 mo period ending in summer 1993 compared with the 6 mo period ending in winter 1993. Allowing for the number of SK that were treated in this time (42 in men, four in women), men experienced an even greater increase in SK numbers, whereas there would have been little change in the percentage reduction in SK numbers in women.

SK incidence Overall, a total of 614 incident SK were diagnosed over 12 mo: 549 in men (89%), and 65 in women (11%), with 24 men (53%, 95% CI 39%–68%) and 13 women (30%, 95% CI 16%–43%) developing at least one incident SK in that time (**Table III**). In general, the number of subjects with incident SK, and the total number of incident SK, were higher in the older age groups in both sexes, with the majority of all incident SK occurring in men and women aged between 60 and 69 y at baseline. Among subjects with baseline SK, 84% of men and 69% of women developed incident SK in 1 y, compared with only 15% of men and 7% of women without SK at visit one. Subjects with baseline SK also accounted for the majority of incident SK: 529 of the 549 incident SK (96%) in men, and 59 of the 65 incident SK (91%) in women. The distribution of incident SK by site is shown in **Fig 1**. In contrast to the distribution of prevalent SK, incident SK occurred more frequently on the head and neck in both sexes. There was also a difference in the site distribution of incident SK between the sexes, with 56% of incident SK occurring on the head and neck in men, compared with 80% in women.

SK regression Regression was recorded separately for prevalent SK and incident SK, because of a postulated relationship between the length of time an SK is clinically present and its subsequent regression (if this occurs).

In total, 346 prevalent SK (74%) regressed in 35 individuals (85%, 95% CI 75%–96%) when monitored over 12 mo. The percentage of SK regressing decreased with age in women, whereas no such trend was detected in men. Although the absolute number of regressed SK was always higher in men than women, the overall percentage of SK regressing was similar (72% *vs* 81%) in 12 mo. The site distribution of regressed prevalent SK is shown in **Fig 1**. SK on the hands or forearms were more likely to regress than those on the head and neck on both men (75% *vs* 67%) and women (87% *vs* 71%).

Prevalent SK were far more likely to regress than incident SK (regression rates 74% and 29%, respectively). A total of 180 incident SK regressed in 31 individuals (84%, 95% CI 72%–96%)) in the study period (**Table IV**). The percentage of incident SK regressing rose with increasing age in men; however, the percentage of men with regressed lesions appeared to fall in those aged 60–69 y. In women, no trend in the percentage of SK regressing was noted, but the percentage of individuals with regressed lesions rose with age (χ^2 for trend = 5.8; p = 0.02). The overall percentage of incident SK regressing was slightly higher in women compared with men (39% *vs* 28%). Incident SK occurring on the head and neck in men were more likely to regress than those on the hands and forearms (37% *vs* 17%), whereas no site difference was detected in women (39% on both) (**Fig 1**).

Median time to regression To estimate the average life span of SK, the median time to regression was determined. Because median time to regression is a function of both the frequency and length of follow-up, a better measure of the regression potential of SK is the number of regressions per SK wk-at-risk. The contribution of any SK to SK wk-at-risk commenced from its date of appearance (assumed to be the date of diagnosis for prevalent lesions, and the midpoint between the date of diagnosis and the previous examination date for incident lesions), and continued until it regressed, was treated, the subject withdrew, or the date of the final examination.

More prevalent SK regressed per 100 SK wk-at-risk in men being seen 6 monthly (2.7) than among women (2.2). Among subjects being seen 2 monthly, however, women had the higher number (6.6 regressions per 100 SK wk-at-risk *versus* 4.5 regressions per 100 SK wk-at-risk in men) (**Table V**). This same pattern was seen with respect to incident SK, although the number of regressions was generally lower.

SK recurrence In the 12 mo follow-up, a total of 53 of the 346 prevalent SK (15%) that regressed subsequently recurred. The percentage of SK recurring increased with age in women, but in men remained fairly static at 16%–20% in each age group. SK were more likely to recur in men than in women, with recurrences equally likely on the head and neck or on the hands and forearms (**Fig 1**). Because analyses were restricted to data from three visits, there was no opportunity to follow up incident SK that had regressed for later recurrence.

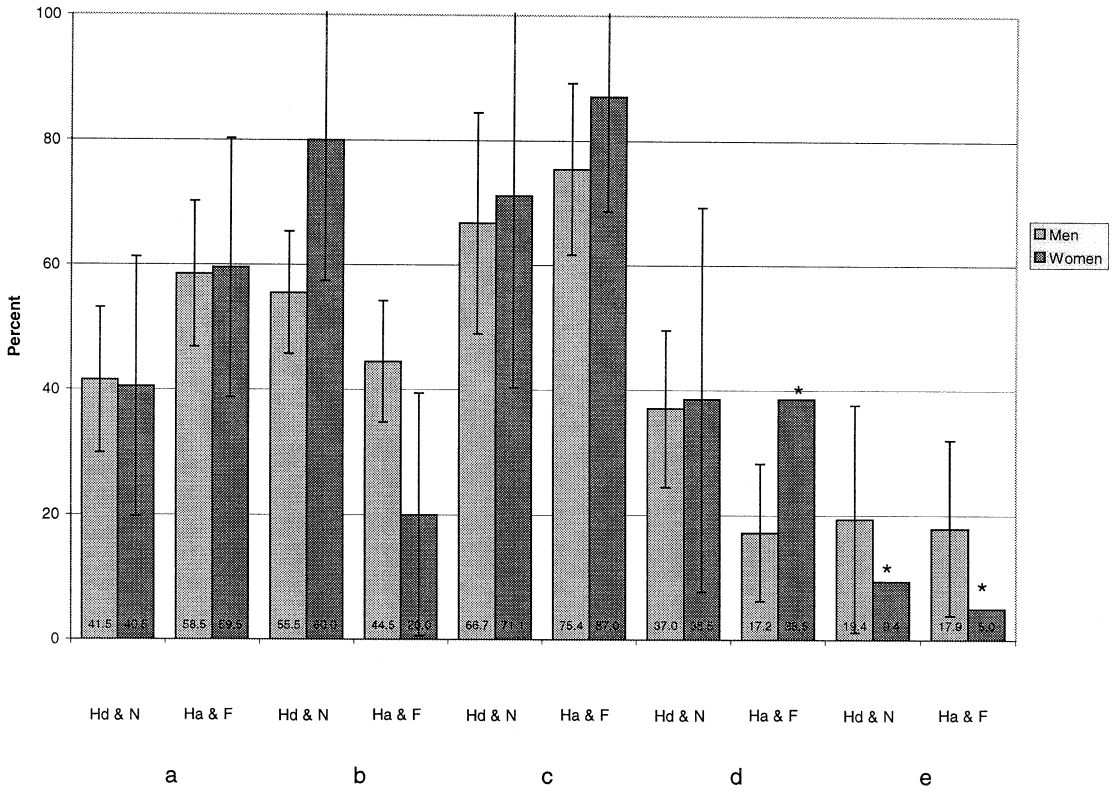

Figure 1. Site distribution of SK according to their status after 12 mo follow-up. Prevalent SK (*a*) are more common on the hands and forearms than the head and neck, but the reverse is true for incident SK. (*b*) Females have more incident SK on the head and neck than males, but fewer on the hands and forearms. Sites of regressed prevalent (*c*) and incident (*d*) SK reflect the sites of prevalent (*a*) and incident (*b*) lesions, except that regression of SK occurs more frequently among females than males. Recurrent SK (*e*) are seen more often in males than females, though equally on head and neck and on hands and forearms. *Bars* represent the percentage of all SK that are on the specified site. Hd & N, head and neck; Ha & F, hands and forearms. Bars with an asterisk represent those estimates where no CI was calculated because of the small sample sizes and the clustering effect.

Table III. Number of incident solar keratoses by sex and age group[a]

Age group (y)	Males (n = 45)	No. of incident solar keratoses (n = 549)	Females (n = 44)	No. of incident solar keratoses (n = 65)
30–39	2	17	1	2
40–49	6	161	2	3
50–59	5	94	3	19
60–69	11	277	7	41

[a]The data are based on 89 residents of Nambour who developed at least one incident solar keratosis over a 12 mo period.

Table IV. Number of regressed incident solar keratoses by sex and age group[a]

Age group (y)	Males (n = 21)	No. of regressed solar keratoses (n = 155)	Females (n = 10)	No. of regressed solar keratoses (n = 25)
30–39	2	2	0	0
40–49	6	25	1	2
50–59	5	54	2	5
60–69	8	74	7	18
		$p = 0.09^b$		$p = 0.02^b$

[a]The data are based on 31 residents of Nambour with at least one incident solar keratosis which also regressed over a 12 mo period.

[b]Chi-square test for age trend in the percentage of participants with regressed incident solar keratoses.

DISCUSSION

We have monitored the natural history of SK in a unique community-based study. During the course of 1 y there was a very high turnover of SK with large numbers developing, regressing, and recurring, especially in those subjects diagnosed with SK at baseline. Although the spontaneous disappearance of SK has been reported previously (Marks *et al*, 1986; Harvey *et al*, 1996a), their underlying lability has not been monitored and reported before, especially in a community rather than a patient sample.

The overall and sex-specific SK prevalence rates presented here are broadly consistent with those reported in another Australian study carried out at similar latitudes (Holman *et al*, 1984) although differences in study design prevent strict comparisons. The increase in the total number of SK (23%) is also comparable to that previously recorded in Australia (22%) (Marks *et al*, 1986). Sex-specific figures were not reported, so it is not known whether this increase masks an apparent sex-specific difference as identified in our study. The SK incidence and SK regression rates, however, were generally higher in our study than previously reported in Australia. Marks *et al* (1986) reported the development of incident SK in 60% of subjects with prevalent SK and in 19% of subjects without SK at baseline, and documented spontaneous remission in 26% of prevalent SK. More frequent follow-up may account for some of the variation in results. For example, if the 6-monthly visit in the Nambour study were ignored and the number of incident and regressed SK was recalculated, 180 SK that were incident at 6 mo and that subsequently regressed by 12 mo, and 53 SK that had regressed at 6 mo and then recurred, would not have been

Table V. Time to regression and rate of regression of prevalent solar keratoses varies with frequency of follow-up

	No. of males/ females	No. of regressed solar keratoses	Median time to regression (w)[a]	Range[b]	Rate of regression (no./Skwar)[c]
6 monthly follow-up					
Males	15	186	162.0	11.3–88.3	2.7
Females	6	43	13.9	0.14–84.4	2.2
2 monthly follow-up					
Males	7	192	10.7	0.14–65.3	4.5
Females	8	73	9.7	2.9–65.6	6.6

[a]Time to regression for each prevalent SK was calculated as the difference between the date diagnosis and the estimated date of regression. The estimated regression date was mid-way between the date of the visit preceding regression and the date of the visit which recorded the regression.
[b]Range = shortest time to regression – longest time to regression.
[c]Skwar is no. of solar keratoses weeks at risk, and was estimated as the number of regresseed prevalent SKs divided by the total time to regression in weeks, multiplied by 100.

documented. This in effect would reduce the percentage of subjects with and without prevalent SK at baseline who developed incident SK to 71% and 6%, respectively. It would also reduce the percentage of prevalent SK that regressed to 60% – still considerably higher than the figure reported by Marks *et al* (1986). Differences in the study populations are another potential explanation for the disparity in the results. The volunteers in the Victorian study with baseline SK may have had more severe disease (and potentially higher rates of regression), whereas a higher percentage of those initially found to be lesion free may have had a past history of SK. Within the Nambour SK study, subjects without baseline SK but with a self-reported past history of SK were five times more likely to develop incident SK than those subjects without such a history. The reported differences may be accounted for by confounding by sex and/or age. Alternatively, a true difference may exist, related to known risk factors such as skin type and ultraviolet exposure. The last theory may also account for the lower SK prevalence (23% of individuals) and regression rates (21% of SK) reported in the South Wales skin cancer study (Harvey *et al*, 1996a; 1996b). No SCCs were diagnosed at the site of a previously documented SK among any of the participants in this study. In view of the low malignant transformation rate (less than 1 in 1000) previously documented by Marks *et al* (1988), however, this is not surprising.

At the gross anatomic level the distribution of prevalent SK was similar in men and women, with approximately 40% of SK diagnosed on the head and neck, and the remaining 60% located on the hands and forearms. The site distribution was reversed for incident SK, suggesting that a higher proportion of facial SK regress, or that they have a shorter life span than SK on the hands and forearms. Although both these theories were supported under certain circumstances (e.g., the percentage of SK regressing was higher on the head and neck than on the hands and forearms in men, but not in women), more work in this area is needed to substantiate these findings. More research is also needed to determine whether these features are intrinsic to SK on these sites, or whether they relate to sex- or site-specific differences in sun protection.

The accurate documentation of the number of SK on the head and neck, hands and forearms revealed a highly skewed distribution, and identified a small percentage of highly susceptible individuals who carry the major burden of SK in the community. Individual variation in SK burden has previously been estimated in a series of Queensland regional studies conducted 30 y earlier in a sample of 1733 residents aged 21 y or over (Silverstone and Gordon, 1966). As a maximum of 10 SK per site was recorded, however, and ''cured'' lesions were included, the findings of the former and present studies are not comparable.

Observation bias was minimized as far as possible by adhering to standard diagnostic criteria when documenting SK, and the validity of clinical diagnoses in this study was high when formally assessed against histologic diagnosis. Further support of diagnostic validity is given by the similarity between the prevalence reported in the current study and that reported in the original prevalence survey based on dermatologists' clinical diagnoses (Green *et al*, 1988).

In summary, these results show that in a community setting SK exhibit very high turnover and that a small percentage of susceptible individuals carry the major burden of SK. Although the study size was small, the results presented here are believed to be the most detailed representation of the natural history of SK over a 12 mo period that is presently available. Study of the mechanisms and determinants of SK regression has the potential to give insight into the possible strategies for control of skin cancer.

This study was supported by the Public Health Research and Development Committee of the National Health and Medical Research Council of Australia. The computer program that permitted the superimposition and comparison of successive skin grid-maps was developed in consultation with Mr. John Pfitzner. We particularly thank the study participants and their doctors for their generous cooperation and support throughout the trial. Thanks also to David Purdie and Steven Darlington for their computing and statistical assistance.

REFERENCES

Cochrane W: *Sampling Techniques*, 3rd edn. New York: John Wiley, 1977, Chapter 9

Frost C, Green A, Williams G: The prevalence and determinants of solar keratoses at a subtropical latitude (Queensland, Australia). *Br J Dermatol* 139:1033–1039, 1998

Green A, Battistutta D: Incidence and determinants of skin cancer in a high-risk Australian population. *Int J Cancer* 46:356–361, 1990

Green A, Beardmore G, Hart V, Leslie D, Marks R, Staines D: Skin cancer in a Queensland population. *J Am Acad Dermatol* 19:1045–1052, 1988

Green A, Battistutta D, Hart V, *et al*: The Nambour Skin Cancer and Actinic Eye Disease Prevention Trial: design and baseline characteristics of participants. *Controlled Clin Trials* 15:512–522, 1994

Green A, Williams G, Neale R, *et al*: Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet* 354:723–729, 1999

Harvey I, Frankel S, Marks R, Shalom D, Nolan-Farrell M: Non-melanoma skin cancer and solar keratoses. I. Methods and descriptive results of the South Wales Skin Cancer Study. *Br J Cancer* 74:1302–1307, 1996a

Harvey I, Frankel S, Marks R, Shalom D, Nolan-Farrell M: Non-melanoma skin cancer and solar keratoses II analytical results of the South Wales Skin Cancer Study. *Br J Cancer* 74:1308–1312, 1996b

Holman CD, Armstrong BK, Evans PR, *et al*: Relationship of solar keratosis and history of skin cancer to objective measures of actinic skin damage. *Br J Dermatol* 110:129–138, 1984

Marks R, Foley P, Goodman G, Hage BH, Selwood TS: Spontaneous remission of solar keratoses: the case for conservative management. *Br J Dermatol* 115:649–655, 1986

Marks R, Rennie G, Selwood TS: Malignant transformation of solar keratoses to squamous cell carcinoma. *Lancet* 1:795–797, 1988

Miller DL, Weinstock MA: Nonmelanoma skin cancer in the United States: incidence. *J Am Acad Dermatol* 30:774–778, 1994

Silverstone H, Gordon D: Regional studies in skin cancer. 2. Wet tropical and subtropical coasts of Queensland. *Med J Aust* 2:733–740, 1966

Staples M, Marks R, Giles G: Trends in the incidence of non-melanocytic skin cancer (NMSC) treated in Australia 1985–95: are primary prevention programs starting to have an effect? *Int J Cancer* 78:144–148, 1998